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ORIGINAL ARTICLE

Limiting factors for liver regeneration after a major hepatic resection for colorectal cancer metastases

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Abstract

Background: Chemotherapy before resection of colorectal metastases in the liver is extensively used and has been shown to induce histopathological changes in the liver parenchyma, although little is known about the effect of chemotherapy on liver regeneration. The aim of this study was to determine if pre-operative chemotherapy influences the regenerated liver volume after a major liver resection.

Patients and methods: This retrospective cohort study included 74 patients subjected to a major liver resection for colorectal metastases. Patients were divided into two groups depending on whether they had been treated with chemotherapy less than 3 months before surgery or not. Liver volumes were measured before and 1 year after resection.

Results: Pre-operative chemotherapy reduced volumetric liver regeneration (83 ± 2% versus 91 ± 2%; $P = 0.007$) as compared with patients without chemotherapy. There was a linear correlation between regenerated volume and time interval between the end of chemotherapy to resection ($P = 0.031$).

Conclusions: Pre-operative chemotherapy in patients with colorectal liver metastases negatively affects volume regeneration after a partial hepatectomy. The time interval between chemotherapy and surgery determines the impact of these affects.

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Introduction

Colorectal cancer (CRC) is one of the most common malignancies in the Western world and the third leading cause of cancer-related mortality in both men and women.[1] Between 30% and 50% of patients will develop liver metastases during the course of the disease.[2,3] A resection is currently the only available potentially curative treatment and for patients with resectable liver metastases and renders a 5-year survival rate in the range of 38–58%.[4–7]

One of the current criteria for curative operability of CRC liver metastases is the sparing of adequate liver volume.[8] This implies a remnant liver volume after a resection of at least 25% in healthy livers[9–11] and more than 30–40% in patients with any impairment of liver function.[11,12] Using novel treatment strategies, such as portal vein embolization (PVE), a two-stage hepatectomy and pre-operative chemotherapy, the number of patients who are potential candidates for a resection has gradually increased.[13–16]

By decreasing the tumour size, pre-operative chemotherapy can permit a curative resection in 15–50% of patients who initially presented with irresectable disease.[17,18] Additionally, it may extend progression-free survival and overall survival.[19,20]

Pre-operative chemotherapy also has possible disadvantages. Several previous studies have shown that chemotherapy may induce parenchymal liver injury, such as steatosis, steatohepatitis and a veno-occusive disease termed sinusoidal obstruction syndrome, all reported as predictors for post-operative complications, liver failure or worsened long-term prognosis.[21–25] Moreover, pre-operative chemotherapy could reduce the hypertrophy of the liver after PVE.[26,27]

However, there is little knowledge of the impact of pre-operative chemotherapy on liver regeneration after a major liver resection. A healthy liver regains mass quickly, even during the first week after a major resection, after which regeneration slowly

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declines[28] stopping 6 months to 1 year after a hepatectomy.[29–31] Not at least if a second or repeated hepatectomy is considered, it is of value to evaluate the effect of pre-operative chemotherapy on liver regeneration. The aim of this retrospective study was to assess the influence of pre-operative chemotherapy on the regeneration of liver volume after a major resection for CRC liver metastases.

Methods

Selection of patients

All consecutive patients with CRC liver metastases who underwent a major hepatectomy, i.e. a resection of three or more Couinaud's segments, at Skåne University Hospital, Lund, Sweden, between 2005 and 2010, were identified. By including only residents of the region of Skåne, with a total population of 1.2 million, to ensure readily available follow-up radiology, a cohort of 78 patients was obtained. Four patients were excluded, two owing to death before any follow-up radiology was obtained, one owing to reoperation for liver metastases within 6 months and one owing to an inability to retrieve the pre-operative CT scan, leaving 74 patients for further analysis. Patients were grouped according to if they had (n = 34) or had not (n = 40) received chemotherapy within 3 months before surgery.

Liver volume measurements

Pre- and post-operative liver volumes were calculated using computed tomography or magnetic resonance imaging transversal plane images. The liver contour on all image sections was manually traced and the area was automatically calculated. Each image section area was multiplied with the section thickness (typically 5 mm) to obtain liver volume. The pre-operative images of patients were selected on the basis of the most recent available images prior to the operation. On PVE patients, the most recent available images prior to PVE were selected instead. The patients that had PVE and chemotherapy (n = 9) were embolized 1–3 weeks after interruption of chemotherapy, four patients had additional chemotherapy while awaiting a resection, which was performed 6–10 weeks after the last chemotherapy cycle. Post-operative images were based on images from the closest to 1 year after the operation. No post-operative images closer than 6 months from the operation were selected. Metastasis volume was measured in the same way as liver volume measurement and then subtracted from the liver volume to get the functional liver volume (FLV). The $\%FLV_{post/pre\text{-}op}$ was defined as the ratio of post- and preoperative FLV. Percentage values over 100 represent a larger liver post- than pre-operatively.

Post-operative hepatic insufficiency was defined as a peak post-operative bilirubin >50 µmol/l and a peak post-operative PK(INR) ≥ 1.7.

The body mass index (BMI) was calculated as weight (kg)/height (m^2). In order to analyse if pre-operative liver volumes were influenced by pre-operative chemotherapy, the formula by Vauthey *et al.*[32] based on body surface area (BSA) was used, where BSA (cm^2) = weight $(kg)^{0.425} \times$ height $(cm)^{0.725} \times 71.84$.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 19 (IBM Corp., New York, NY, USA). Tests regarding differences in $\%FLV_{post/pre\text{-}op}$ between groups were performed using two-tailed independent sample t-tests. The $\%FLV_{post/pre\text{-}op}$ distribution was tested with the Shapiro–Wilk test, the result of which indicated this variable is normally distributed. Otherwise, the Mann–Whitney U-test was used to compare continuous data and Fisher's exact test was used for categorical data. P-values <0.05 were considered statistically significant. If not stated otherwise, data are expressed as mean ± standard error of the mean (SEM).

Results

Patient characteristics and peri-operative data are shown in Table 1. The regimens used in the chemotherapy groups are shown in Table 2. In Table 3, liver volumes before and after a resection are shown for the two groups. A linear correlation was found between regenerated volume, expressed as $\%FLV_{post/pre\text{-}op}$ and the time interval between the end of chemotherapy to the operation, as shown in Fig. 1. In Fig. 2, regenerated volumes as functions of patient age are shown for both groups. No differences between groups were found in the ratio of pre-operative FLV and BSA (P = 0.80).

No difference in $\%FLV_{post/pre\text{-}op}$ was found between patients treated with or without bevacizumab (88 ± 6% versus 83 ± 3%; P = 0.43). Patients treated with adjuvant chemotherapy (n = 63) had volumetric liver regeneration, $\%FLV_{post/pre\text{-}op}$, equal to patients not receiving adjuvant treatment (n = 11) (88 ± 2% versus 87 ± 4%; P = 0.76).

Patients who underwent PVE and received pre-operative chemotherapy (n = 9) versus patients receiving pre-operative chemotherapy alone (n = 25) did not demonstrate any significant difference in $\%FLV_{post/pre\text{-}op}$ (89 ± 4% versus 82 ± 4%; P = 0.22).

Patients suffering from post-operative hepatic insufficiency (n = 13, of whom 5 patients were treated with preoperative chemotherapy) demonstrated a significantly lower $\%FLV_{post/pre\text{-}op}$ (79 ± 3% versus 89 ± 2%; P = 0.013) than patients with lower levels of bilirubin and PK(INR) (n = 61).

Table 4 shows in-hospital morbidity after a resection graded according to Dindo *et al.* [33] No difference in total morbidity was found between the groups (P = 0.35). There was zero 90-day mortality

Discussion

In this study, it was found that pre-operative chemotherapy before a major liver resection results in diminished regenerated liver volume. The impact of pre-operative chemotherapy on post-resectional liver volume has previously only been investigated to a limited extent. Tanaka *et al.*[34] concluded that volumetric liver

Table 1 Patient characteristics and peri-operative data

	No chemotherapy	Chemotherapy	*P*
No. of patients	40	34	–
Sex (male/female)	21:19	19:15	0.82
Age (years)	66 (46–86)	62 (42–74)	0.003
BMI (kg/m^2)	26.5 ± 0.8	24.0 ± 0.4	0.010
No. of diabetes patients	6	4	0.75
Metastasis volume (ml)	66 ± 18	29 ± 9	0.08
No. of metastases	2 (0–5)*	2 (0–7)*	0.74
Size of largest metastasis (mm)	48 (0–120)*	25 (12–99)*	0.30
No. of patients with PVE	1	9	<0.0001
No. of chemotherapy cycles		7 (2–28)	
Time to surgery after chemotherapy (days)		40 (20–88)	
Type of resection (n)			
Right-sided hepatectomy ± atypical resection	26	21	0.18
Extended right-sided hepatectomy ± atypical resection	5	8	0.10
Left-sided hepatectomy ± atypical resection	9	5	0.30
Operative bleeding (ml)	700 (100–15000)	1000 (250–4000)	0.21
Length of hospital stay (days)	8 (5–79)	9 (5–19)	0.69
Peak post-operative bilirubin (μmol/l)	32 (12–202)	35 (13–127)	0.77
Peak postoperative PK(INR)	1.6 (0.9–2.1)	1.6 (1.1–2.6)	0.44
Time from operation to post-operative image (days)	326 (127–822)	315 (188–593)	0.45

Data are presented as either mean ± standard error of the mean (SEM), or median (range). BMI, body mass index; PVE, portal vein embolization. *Based on pathological-anatomic diagnosis.

Table 2 Chemotherapy regimen combinations

Chemotherapy regimen	Number of patients
5-FU + oxaliplatin	17
5-FU + oxaliplatin + bevacizumab	6
5-FU + oxaliplatin + panitumumab	2
5-FU + oxaliplatin followed by 5-FU + irinotecan	2
5-FU + irinotecan	4
5-FU + irinotecan + cetuximab	2
Other combination	1

5-FU, 5-fluorouracil.

regeneration after mainly minor liver resections was unaffected by pre-operative chemotherapy. The fact that only major liver resections were included in this study could account for this discrepancy, as differences in regeneration are more likely to be displayed if there is a greater total volume gain.[35] In addition, the time period from the last chemotherapy cycle to a resection, as shown in this study to be of importance, was not reported in the study by Tanaka *et al.* [34] As interest was in evaluating the final regenerative response, it was choosen to compare liver volumes before a resection to the volumes attained 1 year after the resection, when the regeneration process is completed.[29]

The influence of chemotherapy on liver regeneration has been more thoroughly investigated in conjunction with portal vein occlusion in preparation for major liver resection, where most investigators have found no impact of chemotherapy[36,37] although reduced volumetric regeneration has been found with prolonged chemotherapy.[27,38] The time interval between the ending of chemotherapy and portal vein occlusion has not been implicated in reducing regeneration.[39]

The importance of chemotherapy-induced parenchymal lesions on liver regeneration is yet unknown. As no investigation regarding the histology of tumour-surrounding liver parenchyma was made in this study, speculation about the possibility that chemotherapy-treated patients with histopathological parenchymal transformations also had impaired liver regeneration after hepatectomy can only be made. Earlier studies have demonstrated that chemotherapy-treated patients are at a risk of developing pathological changes in their livers.[23–25] It seems that many of these lesions are reversible, as it has been shown that a correlation exists between the presence of chemotherapy-induced lesions and the interval between the cessation of chemotherapy and resection.[40,41] Pre-operative chemotherapy increased post-operative morbidity in the study by Nordlinger *et al.*,[19] where a resection was performed a median of 4 weeks after the last chemotherapy cycle. Welsh *et al.*[42] found that a prolonged time period from stopping chemotherapy to a resection resulted in a reduction in surgical complications although no influence on total morbidity was found. It is conceivable that a reduced regenerative capacity of the liver after neoadjuvant chemotherapy as found in this study is

Table 3 Liver volumes

	No chemotherapy	Chemotherapy	*P*
FLV before resection (ml)	1521 ± 50	1556 ± 47	0.64
ΔFLV (ml)	–135 ± 35	–278 ± 32	0.005
$\%FLV_{post/pre\text{-}op}$	91 ± 2	83 ± 2	0.007

Data are presented as mean ± standard error of the mean (SEM). Functional liver volume (FLV) signifies functional liver volume. ΔFLV denotes the paired volume difference in FLV between after and before resection. $\%FLV_{post/pre\text{-}op}$ is defined as the ratio of post- and pre-operative FLV.

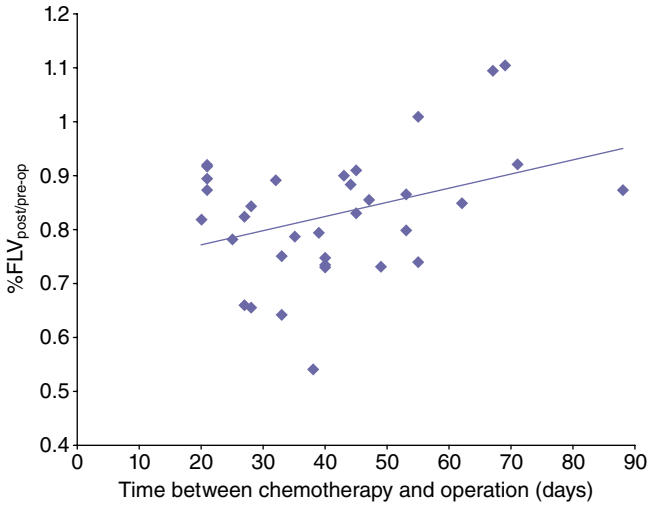

Figure 1 Correlation between regenerated volume and the time interval between cessation of chemotherapy and the operation. A linear correlation was found ($r = 0.37$, $P = 0.031$)

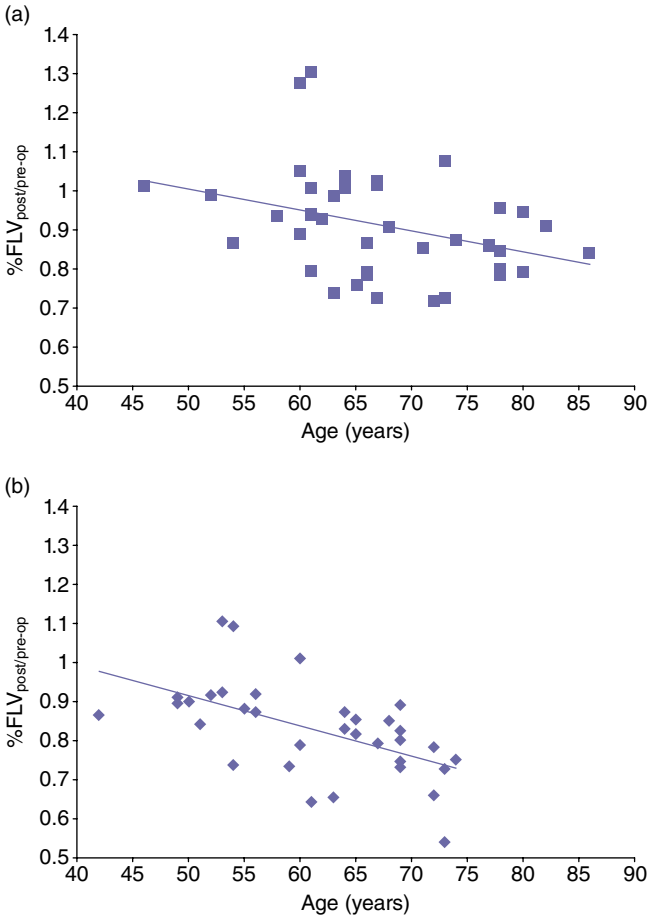

Figure 2 Regenerated volume as a function of the patient's age for groups without chemotherapy (a) and with chemotherapy (b). There was a negative linear correlation between parameters in groups ($r = –0.36$, $P = 0.023$ and $r = –0.558$, $P = 0.0001$, respectively)

associated with an increased post-operative morbidity, although no evidence of this could be found in the present small study.

No measurement of liver volumes before initiation of pre-operative chemotherapy was made. To our knowledge, no investigation on the effect of chemotherapy on liver volume has been made. However, the liver volume is proportional to the liver fat content[43] and chemotherapy has been implicated to cause hepatic steatosis.[23] There exists the possibility that patients treated with pre-operative chemotherapy had an increased liver volume before a hepatectomy. To investigate this, the ratio between the pre-operative liver volume and BSA was calculated[32] and no differences were found between the different study populations, indicating that chemotherapy did not change the pre-operative liver volume. The tumour volume in the non-chemotherapy group was larger as compared with the group with chemotherapy although not reaching statistical significance (Table 1). In the context of portal vein occlusion in preparation for major liver resection, it has previously been shown that a larger tumour volume is associated with an increased volume of the future liver remnant before any intervention.[27] Because the tumour volumes in the present study were relatively small and not significantly different between groups, it is believed that this effect cannot explain the difference in regeneration.

No statistical significant decrease in liver regeneration could be found among patients who underwent PVE compared with patients who did not. These findings match Van den Esschert *et al.*[44] who reported approximately the same degree of regeneration for groups equivalent to the present.

In addition to the findings above, it was also found that patients with a peak bilirubin >50 µmol/l and PK(INR) ≥ 1.7 post-operatively had impaired volume regeneration suggesting a link between post-operative hepatic insufficiency and final

Table 4 Number of patients with Clavien-Dindo grade complications after a liver resection

Clavien-Dindo grade	No chemotherapy	Chemotherapy
0	23	15
1	0	3
2	13	14
3	3	2
4	1	0

$P = 0.35$ when comparing groups with respect to zero complications (Fisher's exact test).

regenerated liver volume. This could indicate that the degree of final liver regeneration is determined shortly after resection.

In this retrospective study, it was found that $\%FLV_{post/pre\text{-}op}$ was on average 83% and 91% among patients treated with and without pre-operative chemotherapy, respectively. The latter number (91%) may seem high, but several previous studies[45,46] have reported similar numbers. Lower numbers are being reported as well, e.g. Nagino *et al.*[31] reporting 74%. Although, in this case, the low number may be explained by patients having injured livers owing to obstructive jaundice, there are studies on healthy livers reporting as low as 83%.[30] The relatively large span of reported percentages is hard to explain and remains to be investigated further.

The limitations of this study include its retrospective design with the inherent problem concerning comparison between groups. For example, previous work show that a higher BMI[34] and age[38] has been linked to weakened regenerative capacity. A negative effect on regeneration of increased age was also found in the present study (Fig. 2). Both BMI and age were significantly lower in the chemotherapy group. This may indicate that the effect of pre-operative chemotherapy on volume regeneration was underestimated in this study. Another limitation is the relatively small number of patients included, and the results require confirmation. In addition, the regimens of chemotherapy were inhomogeneous although oxaliplatin-based chemotherapy was used in 25 out of 34 chemotherapy patients. The type of resection differed somewhat between groups (Table 1), but as inclusion criteria a 'major liver resection' was choosen, defined as resection of 3 or more Couinaud's segments. In a living-donor hepatectomy there does not seem to be any difference in regenerated volume between right- and left-sided hemihepatectomies at 1-year follow-up,[47] justifying the inclusion of different resections.

In this retrospective study volume regeneration was investigated. There are some indications that functional regeneration does not follow the volumetric regeneration.[48] Some previous studies have suggested that functional recovery after a partial hepatectomy takes even longer than volume regeneration.[30,46] Moreover biochemical markers for measuring liver function have been proven insufficient. Shimizu *et al.*[46] showed that functional liver reserve measured with technetium-99 m-galactosyl human serum albumin scintigraphy was lowered for an extended period of time (>6 months). In the same study, full volumetric recovery measured by CT was seen at the end of the first month post-operatively. In future studies, in addition to image volume measurements, it would be interesting to use methods for liver function estimation in studying the effects of chemotherapy on liver regeneration.

Conclusion

It is concluded that in this retrospective study, pre-operative chemotherapy for colorectal liver metastases negatively affects volume regeneration after a partial hepatectomy, the impact being greater the sooner the resection is made after cessation of chemotherapy.

Conflicts of interest

None declared.

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